outstanding in connection with this application were discussed at length and the understanding was arrived at that the instant response would be submitted for the full consideration of the Examiner.

Claims 27 to 29, 31 and 32 are presently pending in the application.

The claims are rejected as lacking patentability under the provisions of 35 U.S.C. 103 over Deng (AQ) in view of Wang et al. (R) and Lin et al. (S). This ground of rejection is deemed to be untenable and is thus respectfully traversed.

The composition of the present invention is an orally administrable composition for the treatment of malaria. Based upon the state of the art as it existed at the time of the present invention, Applicants respectfully submit that it cannot properly be said that such orally administrable composition would have been obvious to those skilled in the art.

In rejecting the claims of the application, the Examiner relies upon the Deng reference as the primary reference. It is urged that Deng discloses that the combination of components has synergistic activity in the treatment of malaria. The Examiner recognizes that the claims differ from the primary reference in specifying the

orally administrable dosage form and in specifying the specific ratios of the compounds in the composition.

The secondary references cited by the Examiner, i.e., Wang et al. and Lin et al., are cited and relied upon in an effort to make up for the deficiencies in the teachings of the principle reference. Thus, it is urged that Wang et al. discloses the formulation of benflumetol in gelatin capsules which are known to be used as an oral dosage form. The Lin et al. reference is relied upon as allegedly teaching the administration of artemether orally as an antimalarial.

Applicants' principle point of contention in respect to the Examiner's rejection involves the Examiner's characterization of the teachings of the Lin et al. reference. Applicants respectfully submit that it cannot properly be said that the teachings of the Lin et al. reference would lead one of ordinary skill in the art to the oral administration of artemether for the treatment of malaria.

Extensive arguments to this effect have been set forth by Applicants in the Response filed October 24, 1995, as well as the Amendment After Final Rejection filed by Applicants on May 20, 1996. The arguments in this respect are incorporated herein by reference and the Examiner is respectfully requested to reconsider those arguments.

Notwithstanding Applicants' arguments to this effect, the Examiner has, in the Official Action of September 16, 1996, maintained the rejection and urges that the teachings of the Lin et al. reference are "suggestive of oral administration".

In derogation of the position taken by the Examiner, Applicants are submitting herewith the additional Declaration of Professor Walther H. Wernsdorfer. In this Declaration, Professor Wernsdorfer, who is an acknowledged expert in the treatment of malaria, analyzes the teachings of the Lin et al. reference. Based upon such analysis, Professor Wernsdorfer concludes that the experiments set forth in the Lin et al. reference do not suggest an oral dosage form wherein the active agent artemether has been formulated.

In the Declaration at page 3, Professor Wernsdorfer initially indicates that the Lin et al. publication incorrectly refers to the oral administration of artemether, and that the performed mode of administering the therapeutic agents, artemether and chloroquine, is, in reality, intragastric gavage.

Professor Wernsdorfer then points out that the *in vivo* experimentation set forth in Lin et al. does not correspond to any established pharmacological model in malariology. This being the case, there is no basis for urging that the reference teachings would suggest to the art-skilled the incorporation of artemether in an oral dosage form for administration in the treatment of malaria.

Professor Wernsdorfer then points out that the testing reported in the Lin et al. reference has to do with the immunological phenomena such as the formation or reduction of serum IgG. However, the doses which were administered to the animals in the testing exceed the art-recognized therapeutic doses of artemether by a factor of about 50 to 100. Such high doses would result in cytotoxic effects by destruction of erythrocytes. This renders the results achieved fully inconclusive since it is not clear whether any observed spleen enlargement is caused by the active agent administered or by the enhanced removal of erythrocytes damaged by the excessive concentrations of the drug.

Professor Wernsdorfer further points out that the high (toxic) amounts administered must have resulted in the death of at least some of the animals, and that this is not reported in the Lin et al. reference.

Professor Wernsdorfer further points out that the high amounts of artemether administered reflect the assumption of poor gastro-intestinal absorption. The poor gastrointestinal absorption of an active agent or active agent composition is not indicative of any suitability for an oral dosage form of the agent. It is also pointed out that the intragastric gavage method of administration of artemether with the suspending agent tragacanth is indicative of the unsuitability of artemether for oral administration by conventional dosage forms such as tablets.

At page 5 of the Declaration and continuing to page 6, Professor Wernsdorfer continues with the analysis of the experiments conducted, and points out serious defects and inconsistencies in the methods which were employed. He points out that in view of the excessive and toxic dose regimens used, the experimentation does not at all reflect any immunological changes which would occur with therapeutic doses of artemether.

Professor Wernsdorfer's conclusions are set forth beginning at page 6 and extending to page 7 of the Declaration. In this respect, it is particularly important to point out that he concludes that the testing reflects a general undesirability of administering artemether via the gastrointestinal tract; the *in vivo* experiments carried out do not relate to the therapeutic use of artemether; and, finally, the experiments do not suggest an oral dosage form wherein the active agent artemether has been formulated.

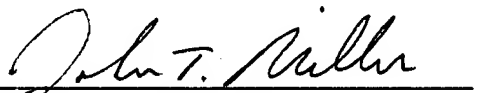
The comments of Professor Wernsdorfer in his Declaration clearly demonstrate that the teachings of the Lin et al. reference would not lead one skilled in the art to conclude that artemether would be effective in an orally administrable dosage form in the treatment of malaria in humans. Further, one skilled in the art could not conclude that artemether would be effective in such oral dosage form in combination with benflumetol for the treatment of malaria.

It is to be noted that in the previously filed Wernsdorfer Declaration submitted with Applicants' Response of January 17, 1995, Professor Wernsdorfer concludes that as of the filing date of the present application, the suitability of artemether for inclusion in solid oral dosage forms was not known. From the presently submitted Declaration of Professor Wernsdorfer and following a full consideration of the teachings of the Lin et al. publication, this conclusion on the part of Professor Wernsdorfer still remains valid since, after consideration of the teachings of the Lin et al. publication, he concludes that the experiments do not suggest an oral dosage form wherein the active agent artemether has been formulated. Applicants thus respectfully submit that the existence of the Lin et al. publication does not, in reality, detract from the patentability of the instantly claimed subject matter. Such subject matter remains clearly patentable over the reference teachings, and the Examiner should now reconsider and withdraw the rejection of the claims.

In view of the foregoing and in view of the evidence submitted herewith, Applicants respectfully submit that the application is in condition for allowance and such allowance is solicited.

Respectfully submitted,

YIQING ZHOU ET AL.

By: 

JOHN T. MILLER
Registration No. 21120

JTM/vca
Washington, D.C.
Telephone No. (202) 371-8850
February 11, 1997